Remarks

Claims

Claims 11, 14, 28-56 and 58-60 are currently pending in the application, with claims 28-56 withdrawn by election of a restriction group. Claims 1-10, 12-13, 15-27, and 61-84 are cancelled. Thus, claims 11, 14 and 58-60 are those currently being examined on the merits. For the Examiner's convenience, a clean copy of pending claims 11, 14 and 58-60 are attached herewith as Appendix A.

Claim 11 has been amended to remove the term "endogenous" in describing the gene to be muted, both in the preamble of the claim and in steps (a), (a)(i), (a)(ii), and (c), and replace it with the term "target". Support for this amendment is found in the specification on p. 3, line 12 and lines 22-23 ("... muting expression of a gene with unwanted activity..."). Applicants would also like to point out that the specification has support for the term "endogenous gene" encompassing the meaning of a gene of a pathogen that may be present in a cell. See, for example, p. 3, lines 11-17 ("wherein the muting nucleic acid includes a sequence homologous to ... a gene of a pathogen. ... Further, the cell is selected from the group consisting of .. a cell infected with a pathogen, for example, wherein a cell is infected with a virus."; p. 4, lines 18-21 ("...provides a method for identifying a muting nucleic acid ... of an endogenous *target* gene... (a) providing a set of fragments of DNA encoding the *target* gene..."); and p. 11, lines 3-7, wherein the term endogenous gene is actually defined to include a gene or gene fragment from a pathogen ("in certain embodiments, an endogenous gene can mean a gene or gene fragment of a pathogen, ... An endogenous gene, whether indigenous to the genome or found in a pathogen, is a *target* for the methods of muting as described herein." – emphasis added). Nonetheless, in the interests of clarity, claim 11 is herein amended to

remove the word "endogenous" from the description of the gene to be muted and insert the word "target". Applicants thus respectfully submit that claim 11, and particularly claim 14, wherein the target gene to be muted is "selected from the group consisting of a collagen, tumor necrosis factor (TNF), *tat*, and an immunoglobulin gene" are definite with respect to 35 USC § 112, para. 2.

Claim 11 was additionally amended to clarify the substep (a)(i), such that it now reads: "(i) [~~designating~~] providing a plurality of DNA compositions that may include regulatory regions and up to the entire sequence [~~as a potential muting nucleic acid composition~~] of the target gene;" This amendment was made merely to clarify the screening process. Support for the "plurality of DNA compositions" in this amendment is found in the application on p. 5, lines 26-28, wherein the description allows for the screening of "a plurality of molecules to obtain a composition capable of muting expression of an endogenous gene..." And, from a general perspective, the entire application provides support for this amendment. All the examples provide support for screening a plurality of DNA compositions for their ability to mute a target gene. That is what the inventors did – they looked for fragments DNA molecules, including the entire target gene itself, to determine which DNA compositions muted the target gene. See the specification, p. 4, lines 18-26 and p.13, lines 25-28 and p. 14, lines 19-28, generally, which indicates that a number of transgene fragments, including the entire target gene, were tested for muting activity; and Examples 2, 6, 9 and 10, which also indicate that a plurality of various gene fragments were tested for muting activity. Although it is implied that the muting DNA compositions will be screened and identified by incorporating them into a recombinant DNA vector library (see p. 4, lines 18-26), it is not

per se required that muting DNA fragments to be inserted into vectors. For example, the specification on p. 3, line 26 through p. 4, line 13, describes a muting nucleic acid that is provided and delivered to a cell such that delivering "is selected from the group of: transforming, transfecting, electroporating, infecting, and lipofecting the nucleic acid into the cell" with no mention of first inserting the muting sequence into a vector being made. Further, in the original claims, it is not until claim 14 that any requirement for placing the muting DNA composition into a vector is included (see original claims 1-14), and p. 3, lines 10-29 of the Summary of the invention also include no requirement for the muting nucleic acid to be incorporated into a vector.

Support for the muting DNA compositions that are screened to include regulatory elements of the target gene is found in the specification on p. 14, lines 24-26 (The 3' portion of α1(I)procollagen gene present in pWTC1 carries some additional *regulatory elements* which effect post-transcriptional muting..."); p. 25, lines 19-21; p. 26, lines 22-28; p. 29, lines 10-16; p. 30, lines 15-18; p. 31, line 19 through p. 33, line 17, particularly p. 32, lines 9-24 ("Muting DNA having HIV-1 genes or gene fragments that carry one or more binding sites for cellular transcription factors NF-κB and Sp1, *or lacking each one or both of these sites*, is provided to an infected cell by transformation... Isolation of the smallest effective length of the muting nucleic acid can be achieved by purification and subcloning of different fragments of HIV-1, starting from within the 5'-LTR ... and extending into the tat gene. *Initially large fragments ... are tested.* Upon obtaining a positive muting response, the active portion can be isolated by subsequent restriction enzyme digestion ... and testing each [fragment] for having a muting activity." – emphasis added). Finally, support is found indirectly, on p. 4, lines 3-7 wherein the

regions of a target gene that could be screened in particular are described generically as "the 5′ untranscribed portion, the coding portion including introns, the 3′ untranslated portion, the 3′ untranscribed portion, and a portion that overlaps the ends of the coding portion..".

Claim 14 has been amended to limit the target gene to "the group consisting of a collagen, tumor necrosis factor (TNF), *tat*, and an immunoglobulin gene." Support for this amendment is found throughout the application (collagen) and in Example 15 on pp. 31 – 33.

Claim 58 has been amended to depend from claim 14 and claims 58 and 59 have been amended to remove "endogenous" from the description of the target gene to be muted and insert the term "target". Support for this amendment is as above for claim 11.

Claim 60 has been amended to depend from claim 14, and has been amended to remove the term "rodent" and replace it with the term "mammalian". Support for this amendment is found in the specification on p. 13, lines 5-6 ("... the phenomenon of "muting expression" was observed in several different types of mammalian cells."); p. 13, line 28 – 29 ("The present examples were conducted in different mammalian cell types..."); p. 32, lines 9-12 (Muting DNA having HIV-1 genes or gene fragments ... is provided to an infected cell...") – i.e., an infected mammalian CNS cell or T-cell, see p. 31, lines 22 and 27, respectively; and in original claim 10.

Applicants respectfully submit that no new matter is added with these amendments.

Finally, claims 57 and 69-84 have been cancelled.

35 U.S.C. § 112, para. 1 – New Matter

As claims 70-79 and 81-83 are now cancelled, the new matter rejections under 35 USC § 112, para. 1 are moot.

35 U.S.C. § 112, para. 2 – Indefiniteness

Claims 58 and 60 were amended to depend from claim 11. Therefore, the indefiniteness rejections under 35 U.S.C. § 112, para. 2 are also moot.

Applicants would also like to take this opportunity to address the discussion regarding the term homology, which occurred during the interview of March 2, 2004. The original claim language contained the phrase "substantially homologous" rather than homologous. In the office action of July 18, 2000 claims 1-27 were rejected for being indefinite because, among other reasons, the phrase "substantially homologous" was asserted do not convey any clear meaning. After an argument to the contrary, presented in Response A filed on December 15, 2000, the rejection of claims 1-27 for reasons of indefiniteness under 35 USC § 112, para 2 were upheld in the office action dated March 14, 2001. Thus, Applicants replaced the phrase "substantially homologous" with "homologous" in the claims submitted with Response B on August 24, 2001, and in the office action of January 30, 2002, the rejections relating to the term "homologous" were withdrawn – see office action of January 30, 2002, p. 12 "The previous rejections of claims *1*-27, 50 and 52 under 35 USC 112, second paragraph is [sic] withdrawn" emphasis added.

Therefore, Applicants respectfully submit that the currently pending claims, as written, are definite.

35 U.S.C. § 102 – Anticipation by Fire et al. (US6,506,559)

As discussed during the interview of March 2, 2004, Fire et al. deals primarily with double stranded RNA, and how such dsRNA sequences inhibit target genes (and see also, the Fire et al. patent throughout, as well as claim 1, for example). The two places in the application that seem to imply involvement of DNA at all are merely theoretical, and propose (A) that the ds-RNA required by the Fire method may be produced *in vivo* from an "[e]ndogenous RNA polymerase of the cell [which] may mediate transcription," (col. 8, lines 63-64) or may be produced from "a transgene *in vivo* or an expression construct, [wherein]a regulatory region ... may be used to transcribe the RNA strand" (col. 8, line 65 through col. 9, line 2); or (B) that "Alternatively [to producing amplified RNA from a gene library] duplex RNA can be produced by *in vivo* ... transcription from an expression construct used to produce the library. The construct can be replicated as individual clones of the library and transcribed to produce the RNA; each clone can then be fed to, or injected into, the cell/organism containing the target gene" (col. 12, line 64 through col. 13, line 3.) Clearly, even if such highly dubious proposals actually resulted in transcription of the correct DNA construct *in vivo*, it is the expression of the construct as ds-RNA that is necessary for inhibition of the target gene in Fire et al., and to produce ds-RNA, two different constructs are required, one for each complementary strand of the intended ds-RNA molecule of interest. Further, Fire et al. discloses *in vivo* transcription of a construct within a bacterial system only, wherein the dsRNA is expressed in bacteria after "cloning a segment of interest between flanking copies of the bacteriophage T7 promoter and transcribing both strands of the segment by transfecting a bacterial strain (BL21/DE3)[28] expressing the T7 RNA polymerase gene from an inducible (Lac) promoter." Once expressing bacteria are produced, they are fed to the nematodes to

provide the nematodes with a source of dsRNA for inhibition of a target gene. See Fire et al., col. 6, lines 21-28; col. 12, line 64 through col. 13, line 3; and col. 17, lines 50-58, for example.

Nothing about the proposals in Fire et al. for possible *in vivo* transcription by some endogenous RNA polymerase, or the actual examples provided, which require transcription of DNA constructs in bacteria to produce inhibitory ds-RNA, followed by ingestion of these expressing bacteria by the nematodes (see again col. 17, lines 50-58 and also the discussion of Figures 5A-5C in col. 21), anticipates the presently disclosed invention, which requires a ds-DNA muting composition that mutes a target gene in an animal system independent of the level of expression of the muting DNA. And just for the record, the actual examples in the presently disclosed invention are for *mammals*, not worms, as in Fire et al. At the time of the filing of the present application, no one had ever succeeded in muting expression of an endogenous gene in a mammalian system – not Fire, not anyone, even with RNAi, in spite of the claims in Fire et al which suggest otherwise.

In light of the amendment to claim 11 to encompass ds-DNA, the discussions which occurred during the interview of March 2, 2003, and the above-detailed arguments, the Examiner is accordingly requested to review and withdraw the rejection of claims based on prior art under 35 USC § 102.

35 U.S.C. § 103 – Fire et al. (US6,506,559) in view of Thomas Jefferson University (WO94/11494)

As discussed in the interview of March 2, 2004, the patent application to Thomas Jefferson University (WO94/11494) was cited in combination with Fire et al. to show that

muting a collagen gene would be obvious to someone of ordinary skill in the art. Given that Fire et al. is not relevant with respect to the muting DNA compositions of the presently claimed invention, it would not be obvious to screen for a ds-DNA composition that mutes a target gene at the level of post-transcription and then mute that target gene by combining the teachings of Fire et al. with the teachings of Thomas Jefferson University. Given the discussions which occurred during the interview of March 2, 2004 and the above-detailed arguments, Applicants accordingly request that the Examiner review and withdraw the rejection of the claims based on prior art under 35 USC § 103.

CONCLUSION

For the reasons stated above, it is respectfully submitted that all pending claims are in condition for allowance. Reconsideration of the claims, consideration of the added claims, and a notice of allowance is therefore requested.

It is believed that a one-month extension of time is needed. Therefore, Applicants hereby petition for a one-month extension for response, and request that account number 19-4972 be charged in the amount of $55 to cover the required extension fee. In the event that additional fees are required for the timely consideration of this application, however, please charge deposit account number 19-4972. The Examiner is again requested to telephone the undersigned if any matters remain outstanding so that they may be resolved expeditiously.

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